IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant	:	Moser, et al.
Appl. No.	:	10/072425
Filed	:	February 7, 2002
For	:	DENDRITIC-LIKE CELL/TUMOR CELL HYBRIDS AND HYBRIDOMAS FOR INDUCING AN ANTI-TUMOR RESPONSE
Examiner	:	Ewoldt, Gerald R.
Group Art Unit	:	1644

LETTER IN RESPONSE TO NOTICE OF NON-COMPLIANT APPEAL BRIEF AND REQUEST FOR CONTINUED EXAMINATION

Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is responsive to the Notice of non-compliant Appeal Brief mailed February 15, 2007 (Notice). A Request for Continued Examination under 37 C.F.R. § 1.114 of U.S. Application No. 10/072,425 is filed herewith so that Attachments D, F, and G of the Evidence Appendix for the Appeal Brief filed June 6, 2006 may be entered into the record. Comments relating to an amendment of the Summary of the Claimed Subject Matter section are also included here.

Remarks/Arguments begin on page 2 of this paper.

REMARKS

Remarks in response to the Notice of Defective Appeal Brief are submitted below. Regarding the reference to US Patent No. 5,851,756 on page 18, this section has been amended to refer to part B and indicate where reference was first cited.

Summary of the Claimed Subject Matter

The Examiner states that the 6 lines at page 28 of the specification are insufficient to support the 12 line method of claim 1. In particular limitations such as the source of the DCs, the preparation of a primary culture of tumor cells, a method for producing a plurality of DC/tumor cell hybrids which include an anti-tumor response and use of autologous or HLA-compatible DCs are not disclosed in the cited sections.

Regarding the source of the DCs, the Appeal Brief has been amended or support is found in sections already referenced as discussed below.

For claim 1, within page 28, lines 20-27, see specifically lines 22, 24 & 25.

For claim 10, the line nos. provided for Embodiments F, G, H & I are incorrect. This has been amended in the twice amended Appeal Brief to "lines 7-23" on page 29. Note that Embodiments F, G, H, & I were referenced in the original Brief, but with incorrect line numbers. This constitutes correction of a typographical error. Attention is directed specifically to lines 9, and 18-19 on page 29.

For claim 21, the section cited does not refer specifically to the source of the DCs. However, claim 10 finds support also in Embodiment C. The Appeal Brief has been amended accordingly.

For independent claim 31, attention is directed to page 29, line 28, and page 30, line 7 within the sections already cited in the Brief.

Regarding preparation of primary cell culture comprising tumor cells, reference is made to page 28, line 21 (claim 1), line 30 (claim 21) and page 29, lines 8 & 17 (claim 10) and page 29, line 26 & page 30, lines 5-6 (claim 31). Preparation of tumor cells is described generally at page 23, line 3 to page 25, line 12. This section has been additionally cited in the Appeal Brief.

The Examiner asserts that the Summary does not disclose a method of preparing a plurality of DC/ tumor cell hybrids. Support for this limitation is included within the

embodiments A-M to which reference has already been given. In some cases, the cited section has been expanded.

For claim 1, see specifically page 28, line 26 (Embodiments A, B, C).

For claim 10, see page 29, lines 11-12 & 20-21.

For claim 21, see page 28, line 26 and page 28, line 32 to page 29, line 1.

For claim 31, see page 30, line 9.

The Examiner states that the use of autologous or HLA-compatible DCs is not disclosed. The Appeal Brief has been amended to refer to page 10, paragraph 3.

Attachments D, F, & G

In the Final rejection of claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29 under 35 U.S.C. § 103(a) based upon Guo, et al. in combination with Sornasse, et al., the Examiner stated that "DC hybridomas retaining T cell activation capability were produced as early as 1981, see, for example, the work of J.H. Peters)" (Final Office Action of September 8, 2005, page 4, lines 8-11). This work of J.H. Peters is not of record in the present application.

Appellants submit herewith a Request for Reconsideration with an Information Disclosure Statement to include the references of the Information Disclosure Statements of 9/9/05 & 10/30/06 referred to by the Examiner in the Notice. This Information Disclosure Statement includes both Peters (1980) and Peters (1981) (Attachments F and G).

Regarding Attachment D, this attachment is a copy of a Declaration by Dr. Moser, one of the inventors of the present application, that was submitted in related application 09/951,849. This Declaration (Attachment D) was included because of its discussion of the Peters (1980) and Peters (1981) references. Appellants' respectfully request that Attachment D be made of record in the present application in order to provide statements from one of the Inventors addressing the Examiner's assertion that DC hybridomas were known at the time of the claimed invention.

Appellants respectfully request that Attachments D, F and G be made of record in this Appeal. An amended (twice amended) Appeal Brief is submitted herewith in which the Evidence Appendix has been amended. Attachments A-G are resubmitted. The Information Disclosure Statement referred to above is also submitted.

Conclusion

Appellants respectfully request that the twice revised Appeal Brief be accepted.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 13, 2007

By: Che S. Chereskin

Che Swyden Chereskin, Ph.D.
Registration No. 41,466
Agent of Record
Customer No. 20,995
(949) 760-0404

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	:	10/072,425
Applicant	:	Moser, et al.
Filed	:	February 7, 2002
TC/A.U.	:	1644
Examiner	:	Ewoldt, Gerald R.
Title	:	DENDRITIC-LIKE CELL/TUMOR CELL HYBRIDS AND HYBRIDOMAS FOR INDUCING AN ANTI-TUMOR RESPONSE
Docket No.	:	DECLE55.1C2CD1
Customer No.	:	20,995

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPEAL BRIEF (twice amended)

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Appeal Brief has been amended (second time) to be responsive to the Notice of Non-Compliant Appeal Brief mailed February 15, 2007. The changes are to page 18 (reference to US Patent 5,851,756). the Summary of the Claimed Subject Matter (pages 6-10) and the Evidence Appendix on page 31.

The Appellant appeals the rejection of Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39 and 41-57 in the above-captioned application. These claims were rejected in a Final Office Action dated September 8, 2005.

This Appeal Brief is being filed in accordance with the rules of 37 C.F.R. § 41.37 and includes a Claims Appendix, an Evidence Appendix, and a Related Proceedings Appendix.

I. REAL PARTY IN INTEREST

The real parties in interest are Vrije Universiteit Brussel and Universite Libre De Bruxelles. The assignment of Kris Thielemans to Vrije Universiteit Brussel is recorded at Reel 012932/ Frame 0166. The assignment of the remaining inventors to Universite Libre De Bruxelles is recorded at Reel 012586/ Frame 0128.

II. RELATED APPEALS AND INTERFERENCES

A pre-Appeal Brief Request for Review and an Appeal Brief has been submitted for related Application No. 09/951,849.

III. STATUS OF CLAIMS

Claims 1-3, 5-14, 16-24, 26-35, 37-57 as listed the Claim Appendix, remain pending. Claims 3, 8, 19, 29, and 40 are withdrawn from consideration. Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39, and 41-57 are the subject of this Appeal.

On September 8, 2005, the Examiner finally rejected Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39, and 41-57.

Prosecution History Of Claims Prior To September 8, 2005 Final Office Action

The above-captioned application was originally filed on February 7, 2002, with Claims 1-57 as a divisional of U.S. Application No. 09/951,849, filed September 10, 2001, which is a continuation of 09/049,502, filed March 27, 1998, abandoned, which is a continuation-in-part of U.S. Application No. 09/025,405, filed February 18, 1998, abandoned, which is a continuation of Application No. 08/625,507, filed March 29, 1996, abandoned, which is a continuation-in-part of Application No. 08/414,480, filed March 31, 1995, abandoned.

On December 28, 2004, when responding to the election of species requirement of November 29, 2004, Appellants elected to prosecute claims pertaining to myeloid origin without amending the claims. However, in the Office Action of March 21, 2005 the Examiner indicated that upon reconsideration, DCs of lymphoid origin were rejoined.

On June 10, 2005, when responding to an Office Action mailed on March 21, 2005, Appellant amended Claims 1, 2, 10, 12, 21, 31, and 47-49. Claims 4, 15, 25, and 36 were cancelled. Claims 3, 8, 19, 29, and 40 remain pending but are withdrawn from consideration.

IV. STATUS OF AMENDMENTS

All amendments have been entered. No amendments have been submitted after the Final Office Action of September 8, 2005.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention relates to methods for producing a plurality of dendritic cell/tumor cell hybrids and methods of producing dendritic cell/tumor cell hybridomas by fusion of tumor cells with dendritic cells (DCs). DC/tumor cell hybrids and hybridomas produced according to the invention are useful in treatment of cancer.

In particular, claims 1-2, 5-7, 9, 42, 46, 50 and 54 are directed to fusion of tumor cells with autologous, HLA-compatible, or allogeneic dendritic cells to produce DC/tumor cell hybrids. These claims are supported generally at page 28, line 20-27 (Embodiments A & B). Preparation of tumor cells is described generally at page 23, line 3 to page 25, line 12. The use of autologous or HLA-compatible DCs is described at page 10, paragraph 3.

Claims 10-14, 16-18, 20, 43, 47, 51, and 55 are directed to fusion of immortalized tumor cells with autologous, HLA-compatible, or allogeneic dendritic cells to produce DC/tumor cell hybridomas. These claims are supported generally at page 29 lines 7-23 (Embodiments F, G, H, and I). Preparation of tumor cells is described generally at page 23, line 3 to page 25, line 12. The use of autologous or HLA-compatible DCs is described at page 10, paragraph 3.

Claims 21-24, 26-28, 30, 44, 48, 52, and 56 are directed to fusion of tumor cells with immortalized autologous, HLA-compatible or allogeneic dendritic cells to produce DC/tumor cell hybridomas. These claims are supported generally at page 28, line 20 to page 29, line 5 (Embodiments C & D & E). Preparation of tumor cells is described generally at page 23, line 3 to page 25, line 12. The use of autologous or HLA-compatible DCs is described at page 10, paragraph 3.

Claims 31-35, 37-39, 41, 45, 49, 53, and 57 are directed to fusion of a tumor cell line that has at least one tumor-associated antigen in common with a tumor sample with autologous, HLA-compatible or allogeneic dendritic cells to produce DC/tumor cell hybridomas. These claims are supported generally at page 29, line 25 to page 30, line 13 (Embodiments J, K, L, and M). Preparation of tumor cells is described generally at page 23, line 3 to page 25, line 12. The use of autologous or HLA-compatible DCs is described at page 10, paragraph 3.

Dendritic cells are defined on page 11, last paragraph. to page 12, first paragraph, as an isolated dendritic cell or its dendritic cell progenitor, preferably derived from bone marrow and

obtained as described in Example 12. In said Example 12, DC fusion partners are prepared by differentiating in vitro proliferating DC precursors isolated from bone marrow.

As is well known, tumor cells generally do not act as antigen presenting cells (APCs) and do not elicit an immune response (page 5, paragraph 1). On the other hand, DCs "are considered as the natural adjuvant of the primary immune response...[and have an] unique ability to sensitize naive T-lymphocytes" (page 9, paragraph 2). The present invention is directed to DC/tumor cell hybrids which harness the ability of a DC to elicit an immune response to provide an anti-tumor response (page 9, last paragraph). Tumor cells obtained from a cancer patient can be fused with a DC to produce a DC/tumor cell hybrid which is administered to the patient where the DC component of the hybrid facilitates an immune response against the tumor.

Example 12 (page 52, line 22 to page 66, line 19) teaches fusion of P815 tumor cells with bone marrow-derived dendritic cells. Out of 50 clones, one clone, hybrid 38, displayed morphological features of dendritic cells (page 58, 1st and 2nd full paragraphs) and also expressed characteristics of the P815 tumor cells such as expression of P1A (page 58, last paragraph to page 59 first paragraph). This clone represents a successful fusion between a dendritic cell and a tumor cell. The dendritic cell is derived from bone marrow and is not a T-lymphocyte or B-lymphocyte. The method used for Example 12 corresponds to the methods relating to independent claim 10.

Hybrid 38 (as well as bone marrow derived DCs) was successful in inducing a primary immune response including activation of naive T-cells As expected, the P815 tumor cells were not able to induce a primary response in vitro (page 59, first full paragraph).

Injections of the hybrid 38 cells into mice inoculated with a lethal dose of P815 tumor cells, protected the mice in 55% of the test animals (page 60, paragraph 2 and Figure 12), further confirming the immunological properties of the DC/ tumor cell hybrid identified as Hybrid 38. **A.**

Independent Claim 1

Claim 1. (Previously presented) A method for producing a plurality of dendritic cell/tumor cell hybrids which induce an anti-tumor response when applied to a patient causing a reduction of the number of tumor cells in said patient, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) preparing a primary cell culture comprising tumor cells derived from said tumor sample,

(c) providing autologous or HLA-compatible allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood, and,

(d) fusing said dendritic cells with said tumor cells to produce a plurality of hybrids, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte.

B. Independent Claim 10

Claim 10. (Previously presented) A method for producing a dendritic cell/tumor cell hybridoma which induces an anti-tumor response when applied to a patient causing a reduction of the number of tumor cells in said patient, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) preparing a primary culture of said tumor sample to provide tumor cells,

(c) deriving an immortal cell line from said tumor cells to produce immortal tumor cells,

(d) providing autologous or HLA-compatible or allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood,

(e) fusing said dendritic cells and said immortal tumor cells to produce a plurality of hybridomas, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte, and

(f) selecting from said plurality of hybridomas a hybridoma which exhibits at least one characteristic selected from the group consisting of dendritic cell morphology, dendritic-like cell or dendritic cell surface markers, dendritic cell genetic markers and immune cell activation in vitro.

C. Independent Claim 21

Claim 21. (Previously presented) A method for producing a dendritic cell/tumor cell hybridoma useful for the induction of an anti-tumor response when applied to a patient causing the reduction of the number of tumor cells in said patient, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) preparing a primary cell culture comprising tumor cells derived from said tumor sample,

(c) providing an immortal cell line comprising immortal autologous or HLA-compatible or allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood,

(d) fusing said immortal dendritic cells with said tumor cells to produce a plurality of hybridomas, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte, and

(e) selecting from said plurality of hybridomas, a hybridoma which exhibits at least one characteristic selected from the group consisting of tumor cell morphology, tumor cell surface markers, and tumor cell chromosomal and genetic markers.

D. Independent Claim 31

Claim 31. (Previously presented) A method for producing a dendritic cell/tumor cell hybridoma useful for the induction of an anti-tumor response, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) analyzing tumor-associated antigens of said tumor sample,

(c) providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample,

(d) providing autologous or HLA-compatible or allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood,

(e) fusing said dendritic cells with said immortal tumor cells to produce a plurality of hybridomas, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte, and

(f) selecting from said plurality of hybridomas, a hybridoma which exhibits at least one characteristic selected from the group consisting of dendritic cell morphology, dendritic cell surface markers, dendritic cell genetic markers and immune cell activation in vitro.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994, IDS) in view of Sornasse, et al. (1992).

2. Claims 2, 12, 33, 42, 43, 44, 46, 47, and 48 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994, IDS) in view of Sornasse, et al. (1992) as applied to Claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29, and further in view of U.S. Patent No. 5,851,756.

3. Claims 50-52 and 54-56 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994, IDS) in view of Sornasse, et al. (1992) as applied to Claims 1, 4, 5, 6, 7, 9, 10, 11, 15, 16, 17, 18, 20, 21, 22, 25, 26, 27, 28, and 29, and further in view of U.S. Patent No. 5,637,483.

4. Claims 13, 14, 23, and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994, IDS) in view of Sornasse, et al. (1992) as applied to Claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29, and further in view of Reid, et al.

5. Claims 13, 14, 23, 24, 34, and 35 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39 and 41-57 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

7. Claims 21-24, 26-31, 44, and 52 are rejected under 35 U.S.C. § 112, first paragraph as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

VII. ARGUMENT

A. Rejections Under 35 U.S.C. § 103(a) Over Guo, et al. (1994, IDS) in View of Sornasse, et al. (1992).

The Examiner states that Guo, et al. (submitted here as Attachment A) teach production of hybrids/hybridomas by fusion of a bone marrow-derived antigen presenting B cell and a tumor cell. While Guo, et al. do not teach dendritic cells (DCs) as fusion partners, the Examiner asserts that it would be obvious to substitute a dendritic cell for the B-cell of Guo, et al. in view of Sornasse, et al. (submitted here as Attachment B).

1. B-cells are excluded as fusion partners.

The present claims on appeal have been amended to specifically exclude both B-lymphocytes and T-lymphocytes. Note that the present specification at page 11, line 24 suggests that B-cells are not to be used as fusion partners. At page 51, lines 21-24, the specification specifically states that a hybrid produced according to the claimed method did not include a B cell. The presently claimed invention is clearly non-obvious over Guo, et al. as the B-cells of Guo, et al. are specifically excluded. Sornasse, et al. do not provide sufficient motivation to substitute dendritic cells for the B-cells taught by Guo, et al. as discussed further below.

One of ordinary skill in the art at the time of the claimed invention would not be motivated to substitute a DC for the B-cell of Guo, et al. based upon the disclosure of Sornasse, et al. Sornasse, et al. conclude that in vitro antigen-pulsed DCs may be used as a physiological adjuvant in vivo (see Abstract). However, Appellants' method is directed to using DCs as fusion partners with tumor cells, not the use of DCs as a physiological adjuvant. Thus, there is no motivation to combine the references in the manner suggested by the Examiner.

The prior art must suggest the desirability of the claimed invention (see MPEP 2143.01, III).

The fact that the references can be combined or modified is insufficient to establish *prima facie* obviousness. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (Claims were directed to an apparatus for producing an aerated cementitious composition by drawing air into the cementitious composition by driving the output pump at a capacity greater than the feed rate. The prior art reference taught that the feed means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is

drawn into the mixing chamber and is entrained in the ingredients during operation. Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432).

In the present case, Sornasse, et al teach the DCs "may" be used as a physiological adjuvant, but Sornasse, et al. is not using DCs as hybrids with other cells and does not suggest doing so. Guo, et al. only teach B-cell/tumor cell hybrids and does not suggest substitution of the B cells with any other cell type. Neither reference teaches the desirability of using DCs in DC/tumor cell hybrids. Accordingly, the combination of references does not provide any motivation to substitute B cells with DCs. Moreover, it is unpredictable that the desirable property which is the teaching of Sornasse, et al., this capability of initiating an immune response, would be retained after the DC is fused with a tumor cell. Neither reference addresses this point.

Even if there were a suggestion to combine the references, the substitution of DCs for B cells would, at most, be "obvious to try" in view of the teaching of Sornasse, et al. However, there would be no reasonable expectation of success because there is no teaching or suggestion in either reference that DCs could be isolated and combined with tumor cells to produce DC/tumor cell hybrids with anti-tumor activity.

As discussed in section 2a of the Moser I Declaration, previously submitted as Attachment B to the response filed June 10, 2005, for the present application (identical to Declaration I filed for the related application US 09/802,397; submitted here as Attachment C) it was not predictable at the time of the claimed invention that replacing the B-cells of Guo, et al. with DC cells would provide the DC/tumor cell hybrids of the claimed invention because it was known at the time of the claimed invention that fusion of dissimilar cells often resulted in loss of tissue specific traits.

Based upon the teaching of Sornasse, et al. one of ordinary skill in the art might expect DCs to function as a physiological adjuvant. However, Sornasse, et al. provide no basis to expect that DCs would retain their ability to induce an immune response after fusion with a tumor cell. Accordingly, one of ordinary skill in the art would not be motivated to substitute the B cells of Guo, et al. with DCs to obtain DC/tumor cell hybrids. There was no expectation,

based upon the cited references, that DC/tumor cell hybrids could be made and administered to produce an anti-tumor response.

The Examiner also asserts that the specification teaches that methods of fusing the DCs and tumors was an adaptation of a well-known method (Final Office Action, page 6, paragraph 2). While techniques to fuse cells were well known at the time of the claimed invention, DC/tumor cell hybrids capable of illiciting an immune response against the tumor were not known at the time of the claimed invention. It was not predictable at the time of the claimed invention that the fusion product would retain the ability of the DC to initiate an immune response against its hybrid partner which is a tumor cell. Yet this is what Applicants have achieved as exemplified in the present specification (see particularly page 60, line 1 to page 61 line 18 for hybrid 38).

2. The claims are limited to particular sources of DCs

The claims on appeal were amended to specify that the isolation of the DCs is "from bone marrow, lymph or blood", or from dendritic cells prepared "by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood".

The Examiner argues that "only a few of the dependent claims limit the source of the DCs to other than spleen" (pages 4-5 of the Final Office Action, bridging sentence). This is incorrect. All of the present claims are limited to "bone marrow, blood or lymph" (see claims 1(c), 10 (d), 21 (c), and 31 (d)).

Neither Guo, et al nor Sornasse, et al. teach isolation from bone marrow, blood or lymph. Neither Guo, et al. nor Sornasse, et al. teach DCs prepared "by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood" (claims 1, 10, 21, 31). Guo, et al. teach isolation of B-cells from spleen (see page 518, col. 1, last paragraph) and Sornasse, et al. teach isolation of DCs from spleen (see pages 15-16, bridging paragraph). However, the present application teaches that spleen is disfavored as a DC source for fusion with tumor cells. Although Examples 1-6 of the present application are directed to spleen as a source of DCs for DC/tumor cell hybrids, in fact, these experiments only produced a T-cell/tumor cell hybrid, which is outside the scope of the claims on appeal. As taught in the specification at page 66, lines 8-15, "[f]usion experiments have been performed using P815 and dendritic cells

isolated from spleen. The yield of hybrid clones was very low, as compared to fusions between P815 and bone-marrow derived DC, and none of them displayed phenotypic and functional features of dendritic cells, suggesting that fusion partners should be proliferating cells or dendritic cells at a more immature stage." Thus, reflecting the scope of the presently pending claims, the present application clearly teaches away from the use of spleen as a source for DCs for hybrids prepared according to the claimed method. Accordingly, even if one of ordinary skill in the art would have been motivated to substitute the B-cell of Guo, et al. with a DC (and Appellants maintain that the cited references do not provide such motivation), based upon both the disclosures of Guo, et al. and Sornasse, et al., one of ordinary skill in the art would have used spleen as the source of the DCs. As shown by the specification, DCs produced from spleen do not produce DC/tumor cell hybrids. Consequently, there was no reasonable expectation of success in achieving the invention as claimed by following the teachings of the two cited references.

The Examiner states that arguing that spleen is not a good source for DCs is a "particularly curious argument" given the fact that Examples 1-6 are directed to spleen and that this element is not recited in the claims (Final Office Action, page 5, 1st and 2nd full paragraphs). As discussed above, the claims do not include spleen as a source of DCs. While the first 6 examples were directed to spleen as a source for dendritic cells, these experiments were not successful and Appellants concluded that spleen is disfavored as a DC source in the practice of the claimed method. Although Examples 1-6 of the present application are directed to spleen as a source of DCs for DC/tumor cell hybrids, in fact, these experiments only produced a T-cell/tumor cell hybrid. As taught in the specification at page 66, lines 8-15, "Fusion experiments have been performed using P815 and dendritic cells isolated from spleen. The yield of hybrid clones was very low, as compared to fusions between P815 and bone-marrow derived DC, and none of them displayed phenotypic and functional features of dendritic cells, suggesting that fusion partners should be proliferating cells or dendritic cells at a more immature stage." Furthermore, all of the present claims are limited to "bone marrow, blood or lymph" (see claims 1(c), 10 (d), 21 (c), and 31 (d)). There is no recitation of DCs isolated from spleen in the claims on appeal.

As discussed in paragraph 9 of the attached Moser II Declaration, submitted as Attachment C to the Response filed June 10, 2005 (submitted here as Attachment E), spleen and lymph nodes contain a high proportion of differentiated DCs. Appellants discovered that these make poor fusion partners. This was not known by others at the time of the claimed invention but was discovered by the inventors of the present application and is clearly shown in the specification. Examples 1-6 of the present specification also demonstrate that DC/tumor cell hybrids could not be produced using spleen as the DC source.

Spleen cells either do not contain proliferating (differentiating) cells, or such cells are present in a negligible amount. This is consistent with the specification which shows that spleen cells are not a good choice for isolation of DC or DC precursors to make DC/tumor cell fusions. This was not known at the time of the invention which is why the initial experiments were performed (unsuccessfully) using spleen cells. The successful use of other sources such as bone marrow, lymph or blood is shown by the present specification and the Moser II Declaration (see paragraph 9) and is the focus of the claims on appeal.

The Examiner argues that the combined references, in view of what was known in the art at the time of the invention, render the methods obvious and that bone marrow, blood and lymph are the most well-known and obvious sources of DCs (Final Office Action, page 6, paragraph 2). The Examiner's assertion that the use of bone marrow, blood or lymph was an obvious choice for isolation of DCs is made without substantiation. Indeed, all of the references cited by the Examiner teach spleen as a source of DCs. The Examiner further argues that it would have been obvious to use DCs from bone marrow, blood or lymph because a patient would prefer to give blood rather than spleen for isolation of DCs to use according to the claimed method. However, as all of the art cited teaches the use of spleen as a source of DCs, one of ordinary skill in the art would not be motivated to use other sources. It is not the patient's motivation that is at issue, but rather the motivation of one of ordinary skill in the art to substitute DCs isolated from blood, bone marrow or lymph for the DCs isolated from spleen which are taught by Sornasse, et al. As discussed in section 1 above, such motivation is lacking in the combination of references cited by the Examiner.

The Examiner again points out that the specification teaches the use of DCs from spleen to form hybrids (Final Office Action, page 8, 2nd full paragraph). Again, while experiments with

DCs from spleen were carried out, the hybrids produced were not DC/tumor cell hybrids. The specification teaches away from using spleen as a source for DCs and spleen as a DC source is outside of the scope of the claims.

3. Routine experimentation would not lead to the present invention

In the Final Rejection of September 8, 2005, the Examiner argues that routine experimentation and variation in the method of Guo, et al. would be permissible and that "DC hybridomas retaining T cell activation capability were produced as early as 1981, (see, for example, the work of J.H. Peters)" (Final Office Action, page 4, lines 8-11). This statement is demonstrably false. DC hybridomas were **not** known before the filing of Appellants' application, and are certainly not shown by Peters. The Examiner has referred to no evidence other than Peters that DC hybridomas were known. While Peters has not been directly cited here, Peters has been cited in related application US 09/951,849. Peters does **not** teach DC/tumor cell hybrids for a number of reasons including the following:

a. Peters is not an enabling reference.

The reference cited in the related applications, Peters 1981 (Attachment F), is merely an Abstract and does not teach how the DCs were prepared. Peters 1981 refers to Peters 1980 (Attachment G) for details on the characteristics of the DCs used for the DC/tumor cell hybrids of Peters 1981. Both Peters 1981 and Peters 1980 cited therein are Abstracts only and do not contain sufficient detail for an enabling disclosure. The DC cells used in the method of Peters are only defined by their preparation procedure (line 5) and by some of their cellular characteristics (lines 6-7).

b. Peters does not teach cell hybrids prepared by fusing tumor cells to dendritic cells isolated from bone marrow, blood or lymph or to dendritic cells isolated by differentiating in vitro proliferating DC precursors isolated from bone marrow, blood or lymph.

The Peters reference does not describe preparation of the DC cells but refers to a previous publication (see above). This publication (submitted here as Attachment F) described the preparation of DC cells from spleen. The present claims specify that the dendritic cells are isolated from bone marrow, blood or lymph, not spleen. Peters does not teach isolation of dendritic cells from bone marrow, blood or lymph. Spleen cells contain differentiated DCs in

contrast to bone marrow, blood or lymph which contain proliferating DC precursors and DCs at a less mature stage as discussed above. Spleen cells are disfavored in the practice of the claimed invention (see page 66, lines 8-15 of the present specification)

c. Peters does not teach DC/tumor cell hybrids – Moser I Declaration

Dr. Moser is one of the inventors of the present application and is highly skilled in the immunology art as evidenced by the Moser I Declaration originally filed for the related application US09/951,849 (Submitted here as Attachment D). Based upon her review of the Peters 1981 Abstract cited by the Examiner and the Peters 1980 Abstract cited within the 1981 Abstract, Dr. Moser concludes that the hybridomas described by Peters do not have a dendritic cell component. As discussed in detail in the Moser I Declaration at section 2, Peters does not provide any evidence that the alleged DC/tumor hybridomas were made and does not teach how to make DC/tumor hybridomas.

For the reasons given above, Peters does not support the Examiner's assertion that DC/tumor cell hybrids that retain T cell activation characteristics were known at the time of the claimed invention.

4. The use of GM-CSF is nonobvious

The Examiner also argues that the use of GM-CSF in cell cultures is obvious. This refers to dependent claims 2, 12, 33, 42, 43, 44, 46, 47, and 48. As discussed below, Appellants maintain that the use of a cytokine such as GM-CSF is non-obvious because the Examiner has provided no teaching showing the use of a cytokine such as GM-CSF for differentiation of DCs in a method of making DC/tumor cell hybrids. U.S. Patent No. 5,851,756, which is cited below for this teaching (Notice of References Cited mailed 3/21/05, see section VII B), shows proliferation of DCs using GM-CSF, not differentiation.

5. The use of irradiation is nonobvious

The Examiner argues that the use of irradiation is obvious as it is unlikely that any patient would knowingly accept unattenuated or live tumor hybridomas. The Examiner is referring to dependent claims 50-52 and 54-56 which are discussed in a separate ground of rejection below. Appellants do not dispute that irradiation of tumor cells was known at the time of the claimed invention. Appellants maintain that fusion of DCs with tumor cells to produce DC/tumor cell hybrids and hybridomas was non-obvious at the time of filing of Appellants' claimed invention.

6. The present specification teaches DCs from bone marrow, blood and lymph and DCs differentiated in vitro from proliferating DC precursors isolated from bone marrow, blood or lymph.

The Examiner argues that the DCs used to produce clone 38 of Example 12 were not "the proliferating DCs of the claims" (Final Office Action, page 7, 3rd full paragraph). The DC fusion partner of clone 38 (Example 12) corresponds to DCs which were differentiated in vitro from bone marrow precursors through culturing DC precursors in vitro for 10 days (see present specification, page 53, last paragraph). A heterogenous cell population was obtained that included non-proliferating differentiated DCs and, probably to a lesser extent, proliferating DCs. Dendritic cells which are prepared by "differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood" are further supported by the specification (Embodiments B, G, I, K, and M on pages 28-30 and page 66, lines 13-15, for example) and enabled by Example 12 of the specification as discussed above and by the Moser II Declaration.

7. Hybrids prepared from differentiation of proliferating DC precursors are capable of illiciting an immune response

The Examiner argues that proliferating, less differentiated DCs of the claims would not be capable of producing the required response (Final Office Action, page 7, last paragraph). However, this ignores the evidence submitted with the Moser II Declaration.

The Moser II Declaration at paragraph 2 describes proliferation of bone marrow progenitors at different culture times by following various markers. Paragraph 4 describes fusion of early (3 and 4 day of culture) BMDC (bone marrow dendritic cells) compared to fully differentiated BMDCs (9 day culture). The Table in paragraph 5 confirms that the proliferating DC precursors (3 and 4 day of culture) are more efficient in DC/tumor cell fusions. The Moser II Declaration shows that less mature DCs are easier to fuse. Paragraph 6 shows that most of the clones that were fused to cells cultured for 3 days were true hybrids. Testing of 19 true hybrids showed that 13 exhibited strong immunostimulatory properties and 4 exhibited weak immunostimulatory properties (paragraph 8). The Moser II Declaration shows that the DC/tumor cell hybrids produced from DCs that were less mature (3 days in culture) were able to induce an immune response.

Accordingly, the Moser II Declaration provides evidence that claims directed to dendritic cells which are prepared by "differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood" are enabled. Appellants submit that the Moser II Declaration provides clear evidence that DC/tumor cell hybrids produced from proliferating DC precursors are capable of producing an immune response as shown particularly in paragraph 8 of the Moser II Declaration. This evidence directly rebuts the Examiner's assertion that immature DCs would not induce an immune response.

For the reasons given above, the present claims are believed to be non-obvious over Guo, et al. in view of Sornasse, et al.

B. Rejections Under 35 U.S.C. § 103(a) Over Guo, et al. (1994, IDS) in View of Sornasse, et al. (1992) and Further in View of U.S. Patent No. 5,851,756.

As explained in section 4 of the Moser I Declaration, filed for the present application on June 10, 2005 and for the related application US 09/802,397 on November 10, 2003, claims 2, 12, 33, 42, 43, 44, 46, 47, and 48 are patentable over U.S. Patent No. 5,851,756. The '756 patent teaches that GM-CSF promotes proliferation in vitro of precursor DCs (see col. 4, line 63 to col. 5, line 9; col. 13, line 66-67, for example), not differentiation as claimed.

Furthermore, since claims 2, 12, 33, 42, 43, 44, 46, 47, and 48 depend ultimately from claims 1, 10, 21, or 31, which are neither taught nor suggested by the cited references, the invention defined in claim 2, 12, 33, 42, 43, 44, 46, 47, and 48 is also patentably distinguished from the references, alone or in combination.

C. Rejections Under 35 U.S.C. § 103(a) Over Guo, et al. (1994, IDS) in View of Sornasse, et al. (1992) and Further in View of U.S. Patent No. 5,637,483.

U.S. Patent No. 5,637,483 was cited to show the use of irradiation of tumor cells in an anti-tumor vaccine to prevent proliferation of the tumor cells in the patient. Irradiation of tumor cells was known at the time of the claimed invention. However, since claims 50-52 and 54-56 depend from claim 1, 10, and 21, which are neither taught nor suggested by Guo et al in view of Sornasse, et al. as discussed above, the invention defined in claims 50-52 and 54-56 is also patentably distinguished from the references, alone or in combination.

D. Rejections Under 35 U.S.C. § 103(a) Over Guo, et al. (1994, IDS) in View of Sornasse, et al. (1992) and Further in View of Reid, et al.

Reid, et al. was cited to show the use of HAT medium for killing of unfused immortal tumor cells. This technique was known at the time of the claimed invention. However, since claims 13, 14, 23, and 24 depend from claim 10 and 21, which are neither taught nor suggested by Guo et al in view of Sornasse, et al. as discussed above, the invention defined in claims 13, 14, 23, and 24 is also patentably distinguished from the references, alone or in combination.

E. Rejections Under 35 U.S.C. § 112, Second Paragraph.

Claims 13, 14, 23, 24, 34 and 35 are rejected as lacking antecedent basis for "said drug." Appellants assert that the antecedent basis for "drug" is found within claims 13, 23 and 35 in the recitation of "drug-sensitive".

As set forth in MPEP 2173.05(e), the failure to provide explicit antecedent basis for terms does not always render a claim indefinite.

If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid"). Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface. >See *Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359, 61 USPQ2d 1216, 1218-19 (Fed. Cir 2001) (holding that recitation of "an ellipse" provided antecedent basis for "an ellipse having a major diameter" because "[t]here can be no dispute that mathematically an inherent characteristic of an ellipse is a major diameter").

In the present case, Appellants maintain that the present recitation is not indefinite as one could reasonably ascertain that the "drug" to which the immortal tumor cells are exposed is the same "drug" to which the tumor cells are "drug-sensitive." It is not necessary to change "drug-sensitive" to –sensitive to a drug—at its first occurrence in the claim to make the meaning clear to one skilled in the art.

F. Rejections Under 35 U.S.C. § 112, first paragraph – New Matter.

The Examiner states that the original specification and claims do not provide support for reducing the number of tumor cells in a patient in claims 1, 10 and 21 (A); fusion using PEG (claims 9, 20, 30 and 41) (B); and "providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample" in claim 31 (C).

Support for the reduction in the number of tumor cells in a patient (claims 1, 10, and 21) is found in the specification, for example at page 60, paragraphs 1 and 2 which reports that injections of the hybrid cells "prevented the growth of pre-established P815 mastocytoma and provided long term protection." When mice were inoculated with a lethal dose of P815 and subsequently received intraperitoneal injections of hybrid cells, long term tumor protection resulted in 55% of the animals (see Figure 12). In the untreated animals, the tumors grew and killed the animals. The treated mice were also protected against a second tumor challenge (page 60-61, bridging paragraph; Figure 13). More generic descriptive support is found on page 15, second full paragraph, of the present specification which discloses that "the term "activation of immune cells in vivo" refers to the immune rejection of a residual tumor, as measured by its reduction in size and by the survival of the patient, as shown for mice in Example 5C or Example 12.

Support for fusion using PEG (claims 9, 20, 30, and 41) is found throughout the Examples. See Example 3 (page 33, line 23), Example 9 (page 46, lines 21-25) and Example 12 (page 54, line 5). Appellants note that the use of PEG to promote cell fusion is well known and is widely used in the art. One of ordinary skill in the art would know that the use of PEG to promote cell fusion is widely applicable to virtually all cell types and not limited to the specific conditions of Examples 3, 9, and 12.

Support for providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample (claim 31) is found at page 25, lines 8-12, which teaches that "as an alternative, a pre-established immortal human tumor cell line can be used, provided that at least one of the tumor-associated antigens from the patients' tumor cells are matched to these pre-established immortal tumor cell." See also Embodiments J, K, L, and M at pages 29-30. A skilled person knows that, if no common antigen is present between the tumor cell line to produce the hybrid and the tumor cell present in the patient to be treated, the hybrids/hybridomas formed are of no value. Appellants submit that claim 31 is supported and enabled by the specification in light of what would be well within the skill level of one skilled in the art.

G. New Grounds of Rejections Under 35 U.S.C. § 112, first paragraph – New Matter (necessitated by Appellants' amendment).

The Final Office Action of September 8, 2005 asserts that Claims 21-24, 26-31, 44, and 52 are not supported for a method of producing DC/tumor cell hybrids which comprises providing an immortal cell line comprising immortal autologous or HLA compatible or allogeneic DCs by isolation of DCs from bone marrow, lymph or blood or preparing said DCs by differentiating in vitro proliferating DC precursors isolated from bone marrow, lymph or blood.

Appellants believe that this ground of rejection does not apply to claim 31.

In addition to the sections of the specification referred to at page 11, lines 11-16 of the June 10, 2005 response (page 25, lines 13-25, page 28, line 20 to page 30, line 13 and page 66, lines 13-14), Appellants direct attention to the specification at page 26, lines 1-18 which describes (2°) obtaining primary DC cells or DCs differentiated from blood, bone marrow or other tissues by culture in the presence of cytokines, (3°) deriving immortal DCs from primary cultured DCs, and (4°) deriving HAT-sensitive variants of these primary or immortal DCs lines to yield drug-sensitive immortal DCs. The fusion of such immortal DC cell lines is clearly supported on page 28, line 20 to page 30, line 13 as previously submitted.

H. Conclusion

In view of the foregoing arguments distinguishing Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-29, 33, 42-44, 46-48, 50-52 and 54-56 over the art of record, arguments directed to the definiteness of Claims 13, 14, 23, 24, 34 and 35, and arguments that claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-35, 37-39, and 41-57 are fully supported by the specification, Appellants respectfully request that the rejection of these claims be reversed.

Please charge any additional fees, including any fees for additional extensions of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

Dated: March 13, 2007

By: _____

Che Swyden Chereskin, Ph.D.
Registration No. 41,466
Agent of Record
Customer No. 20,995
(949) 760-0404

CLAIMS APPENDIX

1. A method for producing a plurality of dendritic cell/tumor cell hybrids which induce an anti-tumor response when applied to a patient causing a reduction of the number of tumor cells in said patient, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) preparing a primary cell culture comprising tumor cells derived from said tumor sample,

(c) providing autologous or HLA-compatible allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood, and,

(d) fusing said dendritic cells with said tumor cells to produce a plurality of hybrids, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte.

2. The method of claim 1 wherein the dendritic cells of step (c) are produced by culturing said precursors in the presence of cytokines.

3. The method of claim 1 wherein the dendritic cells of step (c) are members of an immortal cell line.

4. (Cancelled)

5. The method of claim 1 wherein the dendritic cell of step (c) is of myeloid origin.

6. The method of claim 1 wherein the dendritic cell of step (c) is of lymphoid origin.

7. The method of claim 1 wherein the dendritic cell of step (c) is an isolated dendritic cell.

8. The method of claim 1 wherein the dendritic cell of step (c) is a dendritic cell progenitor.

9. The method of claim 1 wherein the fusion of step (d) is carried out using PEG.

10. A method for producing a dendritic cell/tumor cell hybridoma which induces an anti-tumor response when applied to a patient causing a reduction of the number of tumor cells in said patient, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) preparing a primary culture of said tumor sample to provide tumor cells,

(c) deriving an immortal cell line from said tumor cells to produce immortal tumor cells,

(d) providing autologous or HLA-compatible or allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood,

(e) fusing said dendritic cells and said immortal tumor cells to produce a plurality of hybridomas, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte, and

(f) selecting from said plurality of hybridomas a hybridoma which exhibits at least one characteristic selected from the group consisting of dendritic cell morphology, dendritic-like cell or dendritic cell surface markers, dendritic cell genetic markers and immune cell activation *in vitro*.

11. The method of claim 10 further comprising selecting from said plurality of hybridomas, a hybridoma which expresses at least one tumor-associated antigen in common between the immortal tumor cells and the tumor against which an immune response is needed.

12. The method of claim 10 wherein the dendritic cells of step (d) are produced by culturing said precursors in the presence of cytokines.

13. The method of claim 10 wherein the immortal tumor cells of step (c) are drug-sensitive, said method further comprising, after step (e), killing unfused drug-sensitive immortal tumor cells by exposure to said drug.

14. The method of claim 13 wherein said drug is hypoxyxanthine-aminopterin-thymidine (HAT).

15. (Cancelled)

16. The method of claim 10 wherein the dendritic cell of step (d) is of myeloid origin.

17. The method of claim 10 wherein the dendritic cell of step (d) is of lymphoid origin.

18. The method of claim 10 wherein the dendritic cell of step (d) is an isolated dendritic cell.

19. The method of claim 10 wherein the dendritic cell of step (d) is a dendritic cell progenitor.

20. The method of claim 10 wherein the fusion in step (e) is carried out using PEG.

21. A method for producing a dendritic cell/tumor cell hybridoma useful for the induction of an anti-tumor response when applied to a patient causing the reduction of the number of tumor cells in said patient, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) preparing a primary cell culture comprising tumor cells derived from said tumor sample,

(c) providing an immortal cell line comprising immortal autologous or HLA-compatible or allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood,

(d) fusing said immortal dendritic cells with said tumor cells to produce a plurality of hybridomas, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte, and

(e) selecting from said plurality of hybridomas, a hybridoma which exhibits at least one characteristic selected from the group consisting of tumor cell morphology, tumor cell surface markers, and tumor cell chromosomal and genetic markers.

22. The method of claim 21 further comprising selecting from said plurality of hybridomas, a hybridoma which exhibits at least one characteristic selected from the group consisting of dendritic cell morphology, dendritic cell surface markers, dendritic cell genetic markers and immune cell activation in vitro.

23. The method of claim 21 wherein the dendritic cells of step (c) are drug sensitive, said method further comprising, after step (d), killing unfused drug-sensitive immortal dendritic cells by exposure to said drug.

24. The method according to claim 23 wherein said drug is hypoxanthine-aminopterin-thymidine (HAT).

25. (Cancelled)

26. The method of claim 21 wherein the dendritic cell of step (c) is of myeloid origin.

27. The method of claim 21 wherein the dendritic cell of step (c) is of lymphoid origin.

28. The method of clam 21 wherein the dendritic cell of step (c) is an isolated dendritic cell.

29. The method of claim 21 wherein the dendritic cell of step (c) is a dendritic cell progenitor.

30. The method of claim 21 wherein the fusion in step (d) is carried out using PEG.

31. A method for producing a dendritic cell/tumor cell hybridoma useful for the induction of an anti-tumor response, said method comprising:

(a) providing a sample of a tumor against which said response is needed,

(b) analyzing tumor-associated antigens of said tumor sample,

(c) providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample,

(d) providing autologous or HLA-compatible or allogeneic dendritic cells by isolation of dendritic cells from bone marrow, lymph or blood, or, preparing said dendritic cells by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood,

(e) fusing said dendritic cells with said immortal tumor cells to produce a plurality of hybridomas, wherein said dendritic cell is not a T-lymphocyte or B-lymphocyte, and

(f) selecting from said plurality of hybridomas, a hybridoma which exhibits at least one characteristic selected from the group consisting of dendritic cell morphology, dendritic cell surface markers, dendritic cell genetic markers and immune cell activation in vitro.

32. The method of claim 31 further comprising selecting from said plurality of hybridomas, a hybridoma which expresses at least one tumor-associated antigen in common between the immortal tumor cells and the tumor against which an immune response is needed.

33. The method of claim 31, wherein the dendritic cells of step (d) are produced by culturing in the presence of cytokines.

34. The method of claim 31, wherein said tumor cells of step (c) are drug sensitive, said method comprising, after step (e), killing unfused drug-sensitive immortal tumor cells by exposure to said drug.

35. The method according to claim 34 wherein said drug is hypoxanthine-aminopterin-thymidine (HAT).

36. (Cancelled)

37. The method of claim 31 wherein the dendritic cell of step (d) is of myeloid origin.

38. The method of claim 31 wherein the dendritic cell of step (d) is of lymphoid origin.

39. The method of claim 31 wherein the dendritic cell of step (d) is an isolated dendritic cell.

40. The method of claim 31 wherein the dendritic cell of step (d) is a dendritic cell progenitor.

41. The method of claim 31 wherein the fusion in step (e) is carried out using PEG.

42. A method of claim 1 wherein the obtained hybrid is further induced to express the dendritic cell characteristics.

43. A method of claim 10 wherein the obtained hybridoma is further induced to express the dendritic cell characteristics.

44. A method of claim 21 wherein the obtained hybridoma is further induced to express the dendritic cell characteristics.

45. A method of claim 31 wherein the obtained hybridoma is further induced to express the dendritic cell characteristics.

46. A method of claim 42 wherein said induction is performed using GM-CSF, IFN,γ, TNF-α or a combination thereof.

47. A method of claim 43 wherein said induction is performed using GM-CSF, IFN-γ, TNF-α or a combination thereof.

48. A method of claim 44 wherein said induction is performed using GM-CSF, IFN-γ, TNF-α or a combination thereof.

49. A method of claim 45 wherein said induction is performed using GM-CSF, IFN-γ, TNF-α or a combination thereof.

50. A method of claim 1 wherein the obtained hybrid is treated to prevent further proliferation before using it for the induction of an anti-tumor response.

51. A method of claim 10 wherein the obtained hybridoma is treated to prevent further proliferation before using it for the induction of an anti-tumor response.

52. A method of claim 21 wherein the obtained hybridoma is treated to prevent further proliferation before using it for the induction of an anti-tumor response.

53. A method of claim 31 wherein the obtained hybridoma is treated to prevent further proliferation before using it for the induction of an anti-tumor response.

54. A method of claim 50 wherein said treatment occurs by irradiation.

55. A method of claim 51 wherein said treatment occurs by irradiation.

56. A method of claim 52 wherein said treatment occurs by irradiation.

57. A method of claim 53 wherein said treatment occurs by irradiation

EVIDENCE APPENDIX

Attachment A: Guo, et al. (1994, IDS)

Attachment B: Sornasse, et al. (1992)

Attachment C: Moser I Declaration filed for the present application on June 10, 2005 as a response to the Office Action dated March 21, 2005 and for the related application US 09/802,397 on November 10, 2003.

Attachment D: Moser I Declaration for US 09/951,849. Submitted with the accompanying Request for continued examination submitted herewith.

Attachment E: Moser II Declaration filed for the present application on June 10, 2005 as a response to the Office Action dated March 21, 2005, and for the related applications US 09/802,397 and US 09/951,849 on February 4, 2005.

Attachment F: Peters 1981 (Peters raised by Examiner in Final Office Action mailed September 8, 2005). A Request for continued examination and Information Disclosure Statement is submitted herewith which includes this reference.

Attachment G: Peters 1980. A Request for continued examination and Information Disclosure Statement is submitted herewith which includes this reference.

RELATED PROCEEDINGS APPENDIX

Appeal Brief in related Application No. 09/951,849. An Appeal Brief was filed on April 28, 2006.

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